WHAT MAKES CLINICAL RESEARCH ETHICAL?

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Disclaimer

- These views are mine and do not necessarily represent those of the Department of Bioethics, Clinical Center, National Institutes of Health, Public Health Service, or the Department of Health and Human Services.

Ethics of Clinical Research

Ethical requirements for clinical research:

- Ethical Challenges
- Historical Examples and precedents
- Framework

Ethics and clinical research

The New York Times

New Drugs Stir Debate on Rules of Clinical Trials

By AMY HARMON, September 18, 2010

"Defenders of controlled trials say they are crucial in determining whether a drug really does extend life more than competing treatments. Without the hard proof the trials can provide, doctors are left to prescribe unsubstantiated hope — and an overstretched health care system is left to pay for it. …

"But critics of the trials argue that the new science behind the drugs has eclipsed the old rules and ethics - of testing them. They say that in some cases, drugs under development… may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering."


Powell's Mission Impossible
TIME
HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO...
HUMAN GUINEA PIGS

Ethics of clinical research

- The goal of clinical research is to generate useful knowledge about human health and illness
- Benefit to participants is *not* the purpose of research (although it does occur)
- People are the *means* to developing useful knowledge; and are thus at risk of exploitation

Clinical research is different from clinical practice in ethically important ways

Different Goals

Different Methods

Different justification for risk to individuals

Ethics of Clinical Research: Lessons From History

- Few rules. Most treatments experimental. Physicians experimented to benefit individuals
- "Utilitarian era" emphasis on benefit to society, inclusion of vulnerable groups
- Examination of the scope and limitations
- Rules and Regulations. Protection of human subjects
- Participation in research as a benefit

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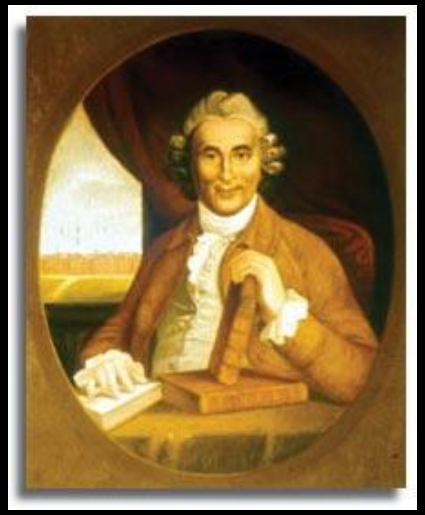
History

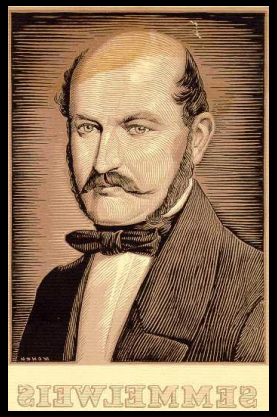
- Lind- British Navy surgeon on the HMS Salisbury in the Channel Fleet

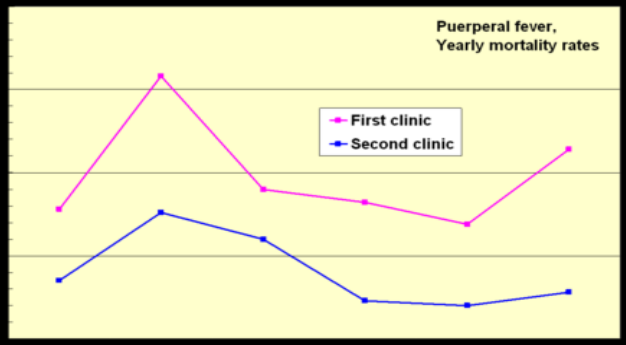


- 1747 first recorded clinical trial (?)

- Lind's evaluation of 6 different interventions on 12 sailors for the treatment of scurvy.

History





- Ignaz Semmelweis
- First noticed a difference in the rates of peurperal fever and death between 2 clinics.
- By careful examination of variables and data collection, concluded that the difference was the type of practitioner (obstetricians versus midwifes) (1841-1846)
- Later, he showed that using chlorinated lime to sterilize obstetricians' hands significantly reduced the rate of puerperal fever. (1847)

History

- Johannes Fibiger (Denmark)
- Controlled clinical trial to test the effectiveness of anti-diptheria serum (1896-97)
- Randomized (based on day arrived) hospitalized patients to receive either standard treatment or standard Plus diptheria serum
- Deaths in serum group 8 of 239 patients, compared to 30 of 245 in the standard treatment group

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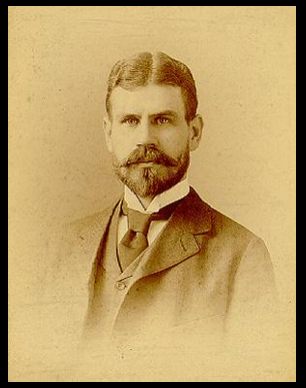
History

- 1897 Sanarelli announced he discovered the bacillus of yellow fever and produced yellow fever in 5 patients.

- 1898 Osler condemns Sanarelli:

  "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."

History



- 1900 Yellow Fever Board established in USA
- 1901 Walter Reed proposed yellow fever research that included:
  - Self-experimentation
  - Written agreements with other subjects
  - Payment in gold
  - Restriction to adult subjects
  - Using the phrase “with his full consent” in all journal articles.

History

- Nazi war experiments
- 1946-49 Nuremberg Trial and formulation of the Nuremberg Code.

History

Medical Research Council Randomized controlled trial of streptomycin for Tuberculosis. (1948)

- Streptomycin 4x/day for the treatment group
- Bed rest alone for control (C) patients
- Both groups observed for 6 months.
- Results:
  - Deaths--4 of 55 (7%) treatment group; 14 of 52 controls (27%)
  - Radiologic improvement --27 of 55 (51%) treatment group; 4 of 52 (8%) control group

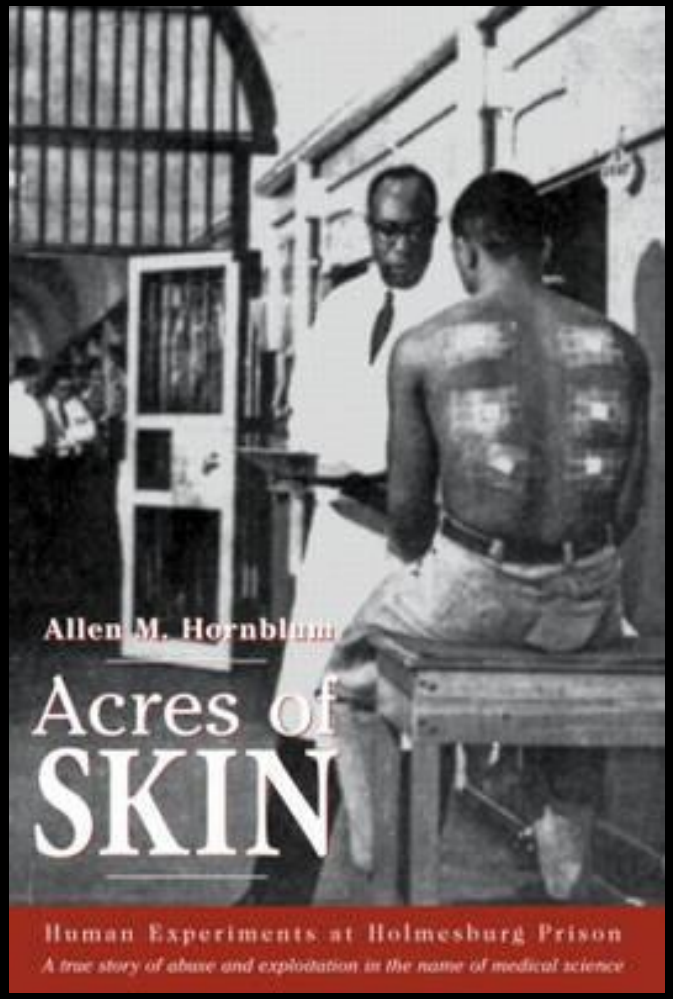
- "The overall results leave no doubt of the beneficial effect of streptomycin."

Salk polio vaccine trials

1954

- Almost 2 million children in the US
- Salk inactivated polio vaccine vs. placebo vs. no vaccine
- 80-90% effective against paralytic polio

Research with prisoners



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History


Henry K. Beecher

- Henry Beecher

- The New England Journal (1966) –
- 22 examples in which patients "never had the risk satisfactorily explain to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered."

History

Beecher's 22 examples included:

- Withholding antibiotics from men with rheumatic fever,
- Injecting live cancer cells into nursing home patients (Jewish Chronic Disease Hospital),
- Transplanting melanoma from daughter to mother who died about a year and half later.

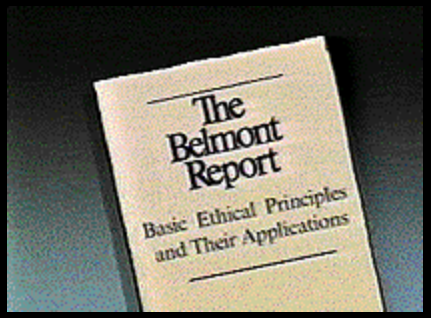
History

USPHS study of syphilis (Tuskegee)

- Study of syphilis in African-American men controls in Macon County Alabama
- USPHS actively tried to prevent men from receiving penicillin
- 1972 press reports caused DHEW to stop the study
- National Research Act and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

History

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research



Ethical principles underlying research:

- Respect for Persons
- Beneficence
- Justice

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U.S. Regulations and Guidelines

- The Common Rule (US 45CFR.46)
- 45CFR.46 Subparts B, C, D
- FDA regulations (US 21CFR50 and 56)

Codes and Guidelines

- Declaration of Helsinki (1964- 2008)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002)
- ICH/GCP-International Conference on Harmonization- Good Clinical Practice (1996)

What makes clinical research ethical?

- Guidance developed in response to historical events
- Some divergent recommendations
- Differences in interpretation
- Need for a systematic, coherent, universally applicable framework

Ethical framework: 8 principles

- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *J Am Med Assoc.* 2000; 283(20):2701-11
Emanuel E, Wendler D, Killen J, Grady C. *J Infect. Diseases* 2004; 189:930-7

Collaborative Partnership

- Ethical clinical research should be a collaborative partnership with the relevant partners, e.g.
  - Collaboration in planning, conducting and overseeing research, and integrating research results into the health system
  - Respect for contributions of partners
  - Collaboration with existing systems of health care

Collaborative Partnership

- Collaborative partnership can be facilitated by:
  - Planning with policy makers and health system
  - Community advisory boards
  - Patient advocates on scientific advisory boards
  - Advocates for research funding
  - Collaborating investigators
  - Information for practicing clinicians
  - Etc.

Collaborative partnership

Valuable Scientific Question

Ethical clinical research should answer a valuable question, i.e., one that will generate new knowledge or understanding about human health or illness, i.e. a socially, clinically, or scientifically useful question

Valuable Scientific Question

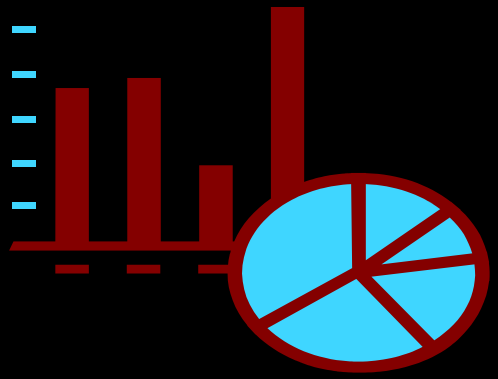
- Valuable to whom?
  - Participants
  - Community in which participants live?
  - Some other group
  - Society, future people etc?
- In whose view?
- How is value to be judged?

Value: A case example

- Phase 3 trial of RV144 prime-boost combination HIV vaccine in Thailand
  - Some disagreement about whether there was sufficient scientific value and confidence in the vaccine product, strategy, design to warrant moving forward? (Science; 2004, 303 Feb- July)
  - Some disagreement about the 'value' of the results (Oct 2009)

Valid Scientific Methodology

- Ethical clinical research should be designed in a methodologically rigorous manner (design, methods, statistical power and methods, etc.) that will yield valid, reliable, generalizable, and interpretable data, and that is feasible



Scientific validity example

- Choice of endpoints
  - e.g. ischemic or hemolytic stroke
- Choice of design
  - Randomized double blinded control
  - Noninferiority or superiority
- Choice of procedures
  - Measures of outcome, length of follow- up
- Statistical methods
  - Power, methods, level of significance
- Feasiblity


THE PUBLIC
THE INDIVIDUAL

Fair subject selection

- Scientific objectives should guide inclusion criteria, recruitment strategies, and selection (not privilege or easy availability or vulnerability)
- Minimize harms and fairly distribute harms and benefits
- No exclusion without justification

Research as burden or benefit?

Research as ‘burden’

Subjects need protection

Research as ‘benefit’

Subjects need access

Fair subject selection: what is the appropriate population?

- Jesse Gelsinger
- Should the study have been done in healthy affected adults with partial OTC deficiency or in severely ill infants with complete OTC deficiency?

Favorable risk-benefit

- Are risks to subjects necessary and minimized?
- Are risks justified by benefit to individual subjects and/or the importance of the knowledge to society?
- Are benefits maximized?

Non-maleficence and Beneficence

Benefits and Risks in Research

[I]nterests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected.

The Belmont Report

Independent review

- To ensure ethical requirements have been fulfilled
- To check investigator biases and conflicts
- To assure the public that research is not exploiting individuals or groups

Criteria for IRB Review (45CFR.46.111 and 21CFR56.111)

- Risks … are minimized.
- Risks are justified by anticipated benefits, if any, to the subjects or the importance of the knowledge to be gained
- Subjects will be selected and treated fairly
- Informed consent is adequate

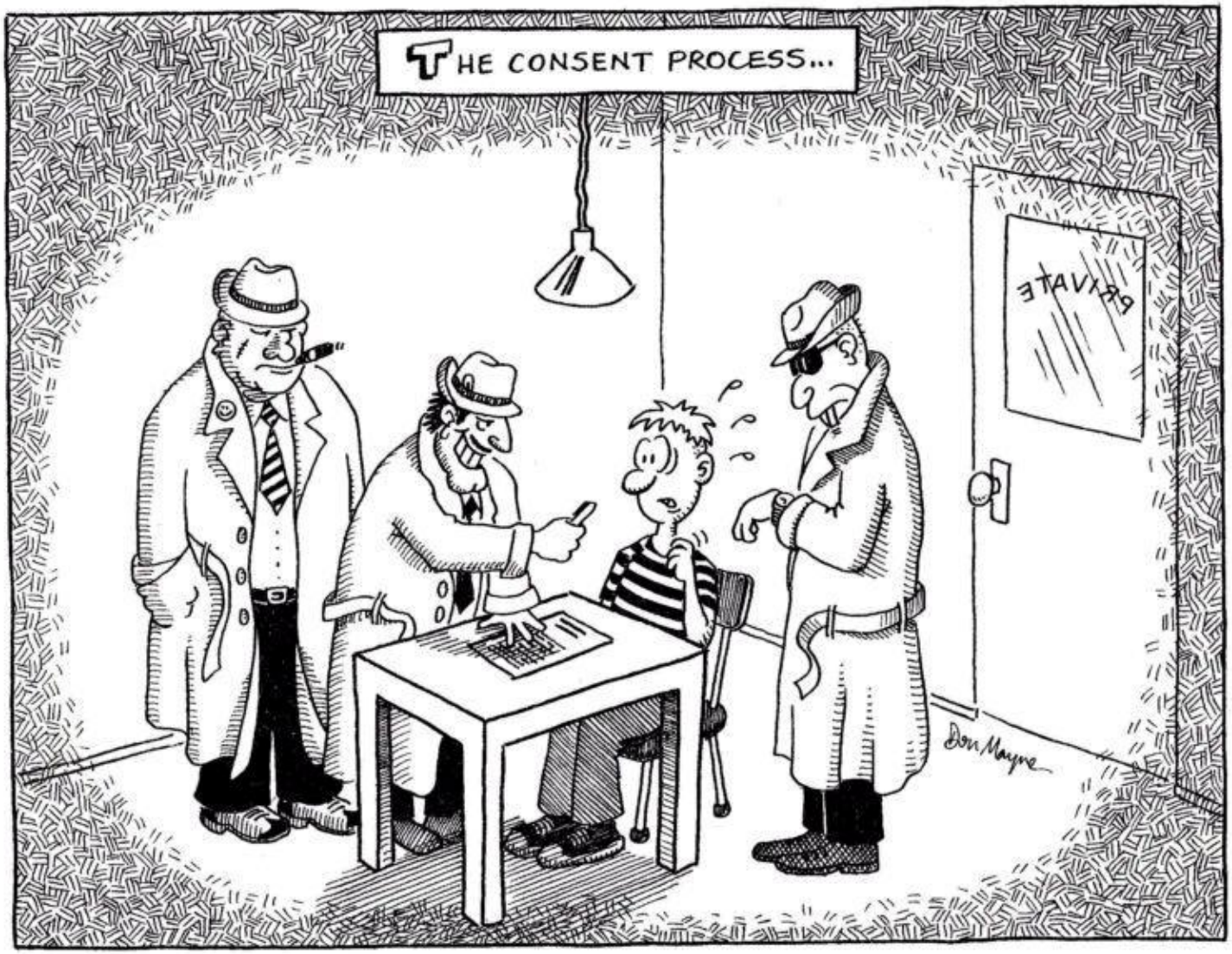
Informed Consent

- Informed consent ensures that individuals have the opportunity to decide whether they want to participate in research or continue participation and whether it is compatible with their goals, values and interests

Respect for persons

Informed consent

- Disclosure of information
- Understanding
- Voluntary decision making
- Authorization



Respect for enrolled subjects

- Ethical research requires continued respect for the rights and welfare of participants throughout research, including:
  - Protecting confidentiality
  - Monitoring welfare
  - Recognizing right to withdraw
  - Providing new information
  - Informing participants of findings
  - Post trial planning

- Collaborative partnership
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- Valid scientific methodology
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Framework

- Systematic and sequential
- Necessary
  - Procedural requirements may be waived
- Universal
  - Adapted and implemented according to context
- Requires balancing, specification

Ethical framework: 8 principles

Conflicts occur between the principles. e.g.,

- Enhancing scientific validity may increase risks.
- What seems necessary to respect enrolled subjects or obtain informed consent may compromise scientific validity.

Ethical framework: 8 principles

In order to apply the principles, reconcile conflicts and make informed judgments about ethical research, need:

- Educated and informed investigators and research teams
- Educated IRBs with diverse members including investigators, statisticians, ethicists, and lay people.